Length-dependent binding of human XLF to DNA and stimulation of XRCC4.DNA ligase IV activity.

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Public Summary:

Scientific Abstract:
An XRCC4-like factor, called XLF or Cernunnos, was recently identified as another important factor in the non-homologous DNA end joining (NHEJ) process. NHEJ is the major pathway for the repair of double-strand DNA breaks. The similarity in the putative secondary structures of XLF and XRCC4 as well as the association of XLF with XRCC4.DNA ligase IV in vivo suggested a role in the final ligation step of NHEJ. Here, we find that purified XLF directly interacts with purified XRCC4.DNA ligase IV complex and stimulates the ligase complex in a direct assay for ligation activity. Purified XLF has DNA binding activity, but this binding is dependent on DNA length in a manner most consistent with orientation of the C-terminal alpha helices parallel to the DNA helix. To better understand the function of XLF, we purified an XLF mutant (R57G), which was identified in patients with NHEJ deficiency and severe combined immunodeficiency. Surprisingly, the mutant protein retained its ability to stimulate XRCC4.DNA ligase IV but failed to translocate to the nucleus, and this appears to be the basis for the NHEJ defect in this patient.